Sponsor Executive Summary

XVIVO Perfusion, Inc.

1 Introduction

STEEN Solution™ is intended to be used with the XVIVO Perfusion System (XPS™) as indicated for use for temporary normothermic (at body temperature) machine ex vivo perfusion and ventilation of excised donor lungs that were initially deemed unacceptable for transplantation. During this perfusion the function of the lungs are periodically reassessed for acceptability for transplantation.

STEEN Solution™ with the XPS™ is the subject of Humanitarian Device Exemption (HDE) application H120003 filed July 10, 2012, and the subject of a review by the Gastroenterology-Urology Devices Panel of the FDA Medical Devices Advisory Committee, in a meeting which is scheduled for March 20, 2014.

A Humanitarian Use Device (HUD) designation for STEEN Solution™ was granted on June 17, 2008.

1.1 Target Population

STEEN Solution™ with the XVIVO Perfusion System (XPS™) is designed to benefit those patients with *end stage lung disease* who are awaiting lung transplant. In 2012, the most recent year for which numbers are published, more than 25% of approximately 1600 patients deemed eligible for the waiting list died without a lung transplant.[1]

1.2 Device Description

STEEN Solution™ is a clear, sterile, non-pyrogenic, non-toxic, physiological, extracellular (low potassium) electrolyte solution containing human serum albumin (HSA) and dextran 40. The solution has a colloid-osmotic pressure (COP) so that during perfusion a physiological pressure and flow can be maintained in the lung without the development of pulmonary edema (fluid accumulation in the air spaces and parenchyma of the lungs).

The XPS™ System was developed by XVIVO Perfusion Inc. as a response on an FDA ruling that STEEN Solution™ could not be approved for marketing without a dedicated perfusion system. The XPS™ system has not been marketed in or outside of the United States as yet. The XPS™ System is an integrated cardiac bypass system comprised of FDA cleared components such as a Maquet CardioHelp centrifugal pump (K102726) and a Hamilton C2 ICU (intensive care unit) pressure-controlled ventilator (K092148).

Appendix I Device Description

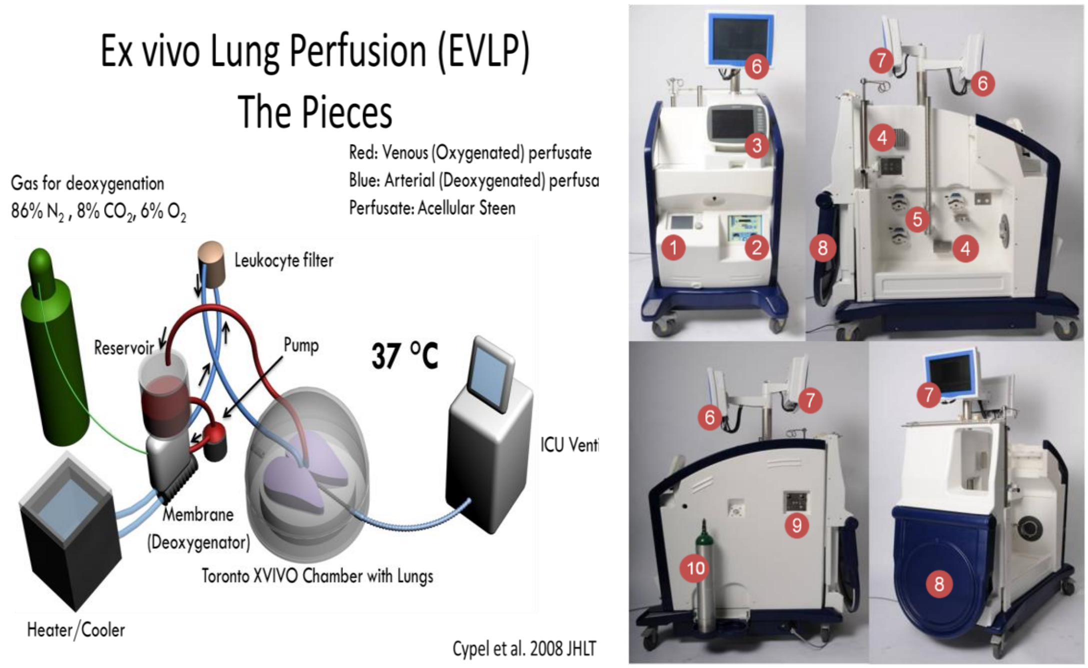


Figure 1 Ex vivo Lung Perfusion (EVLP) and the XPS™ System

Vitrolife AB, parent company of XVIVO Transplantation Systems AB, obtained FDA clearance in 2001 for Perfadex, a Low Potassium Dextran (LPD) solution for rinsing, storage, and transportation of lungs prior to transplant (the business activities of XVIVO Transplantation Systems AB was soon thereafter absorbed into Vitrolife). Perfadex supports cold preservation of donor lungs. The sponsor developed STEEN Solution™ during 1999 through 2000 with the aim of solving the chronic shortage of organs for lung transplantation. STEEN Solution™ was first used in a clinical lung transplantation in 2000. It was CE marked and has been in regular clinical use in Europe for lung transplantation since 2006 and approved for marketing in 2009 in Australia and in 2012 in Canada. STEEN Solution™ with the XVIVO Perfusion System (XPS™) has been used in a U.S. clinical trial under Investigational Device Exemption (IDE) G100104, since March 2011.

Company History & Name Change

1998	XVIVO Transplantation Systems AB started by Dr Magnus Nilsson
1999	XVIVO Transplantation Systems AB was merged with Scandinavian IVF Science AB to form Vitrolife AB which took over operations.
2009	XVIVO Perfusion AB was started as a subsidiary to Vitrolife AB and took over the operations in Europe.
2012	XVIVO Perfusion AB is a separate Corporation from Vitrolife AB and Xvivo Perfusion Inc was started in the U.S.A as a subsidiary to Xvivo Perfusion AB for the operations there.

Table 1 Company History. The sponsor shall be used to refer to the Company due to name changes.

The development of STEEN Solution™ was based on the theory that, following hypothermic transport of donor lungs, normothermic ex vivo lung perfusion (EVLP) could be performed at the transplant center, providing oxygen and nutrients to the donor lung at a physiologic body temperature hence, ending ischemic time. The normothermic perfusion with STEEN Solution™ allows the lung function to be reassessed for transplantation while the lung is in a functioning metabolic state. Table 2 provide the comparison between hypothermic vs. normothermic.

Hypothermic Perfusion	Normothermic Perfusion
• Decreases metabolism • Prevents exchange of oxygen and nutrients = ischemia	• Normalize metabolism • Permits exchange of oxygen and nutrients = no ischemia • Flushes residual donor blood products that remains in the microvasculature

Table 2 Hypothermia vs. Normothermic Perfusion

The sponsor first approached FDA in 2007 to discuss 510(k) clearance of STEEN Solution™ as a warm flush solution to provide a secondary evaluation of the lungs during perfusion in a normothermic environment. At that time the FDA could not identify a predicate device for the normothermic use of STEEN solution since all comparable solutions were approved for hypothermic perfusion and suggested we apply for an HUD designation and an HDE. A Humanitarian Use Device (HUD) designation for STEEN Solution™, was granted June 17, 2008.

In June of 2008 a pre-IDE teleconference was held between the FDA, the sponor, and Dr Keshavjee (Transplant surgeon at Toronto General Hospital) to discuss and receive FDA advice regarding the Toronto HELP study and the "off the shelf" ex-vivo circuit components to be used to perform the EVLP. At this time the FDA discussed the possible creation of a dedicated machine. However the concern by Dr Keshavjee was that creating a dedicated machine would be extremely costly leading to limited centers being able to afford to perform EVLP. He further stated all of the devices needed to perform EVLP were approved and off the shelf (i.e. Ventilator, Cardio-Pulmonary By-pass circuit, heater-cooler unit). The FDA stated they would consider all his key points and further examine the issue.

It was subsequently recommended by CDRH that the sponsor create a dedicated system to perform the perfusion procedure (EVLP) Ex Vivo Lung Perfusion, and conduct a prospective clinical study to support the Humanitarian Device Exemption (HDE) and/or a Premarket Approval Application (PMA). XVIVO collaborated with the FDA on the regulatory pathway toward HDE followed by PMA approval. It was established in the original IDE and subsequent submissions that along with the HELP data XVIVO would submit the first 12 : 12 cohort of patients for HDE review. The reason for the 12:12 cohort was due to the use of various approved off-the shelf products that were used to perform EVLP in the HELP study. Therefore the sponsor needed to provide additional data to show that its device performed with the same functionality in performing EVLP.

An original Investigational Device Exemption (IDE) was submitted to FDA May 28, 2010 to request approval for a prospective, controlled, multicenter US clinical study of STEEN Solution™ used with the dedicated XPS™ perfusion system. The IDE clinical study design was based on the protocol and experience from the HELP study (the clinical study of EVLP with STEEN Solution™ conducted at Toronto General Hospital). The sponsor initiated the US clinical study following IDE approval on April 29, 2011.

2 Worldwide Experience

2.1 Clinical Experience

EVLP with STEEN Solution™ has been independently studied by several international transplant centers. Findings from these independent studies have been published in peer-reviewed journals, and the references are included in the bibliography provided under Appendix X Bibliography. Selected reprints are also available under Appendix II Selected Articles, below are direct links.

A. **Cypel, M., & et al. (2011, April 14). Normothermic Ex Vivo Lung Perfusion. *The New England Journal of Medicine***
B. **B. George T, et al. Lung Transplant in Idiopathic Pulmonary Fibrosis. Arch Surg. 2011; 146 (10): 1204-1209.**
C. **Aigner, C., et al. (2012). Clinical Ex Vivo Lung Perfusion-Pushing the Limits. *American journal of Transplantation***
D. **Wigfield, C., et al. (2012). Successful Emergent Lung Transplantation After Remote Ex Vivo Perfusion Optimization and Transportation of Donor Lungs. *American Journal of Transplantation***
E. **Cypel, M., et al. (2012, November). Experience with the first 50 ex vivo lung perfusions in. *CARDIOTHORACIC TRANSPLANTATION***
F. **Sanchez, P., & Griffith, B. (2014, January 30). International Clinical Experiences with Ex Vivo Lung Perfusion. *ARTIFICIAL ORGAN CT SURGERY (S AKHTER, SECTION EDITOR)***

2.2 Marketing Experience

STEEN Solution™ obtained CE marking in 2006 and became available for use with commercially available cardio-pulmonary by-pass circuit equipment. Australian Therapeutic Goods Administration (TGA) clearance was obtained in 2009. Over 100 EVLP transplants using STEEN Solution™ have been performed in Europe and Australia. Health Canada granted the right for sales of STEEN Solution™ in Canada in 2012. Including the EVLP transplants performed in the clinical trial, Toronto General Hospital has transplanted over 100 patients with lungs reassessed after EVLP. Approximately 100 pre-clinical and/or clinical investigator-sponsored studies using STEEN solution have been published in peer-reviewed publications.

3 Lung Transplant History, Regulation of Donation and Allocation, and Standard Practice

The first lung transplant was attempted in 1963 by James Hardy, M.D., of the University of Mississippi. During the next 20 years, a total of 44 lung transplants were attempted worldwide, none of which were successful. The first successful lung transplant was performed in 1983 by Joel Cooper, M.D. at Toronto General Hospital. The science surrounding lung transplantation has continued to evolve during the last thirty years; including improvement of antirejection drugs, the use of Perfadex® (LPD, Low Potassium Dextran Solution) for flushing the donor lungs and the use of nitric oxide post transplant for pulmonary dilatation . The concept of normothermic perfusion, as performed with the XPS™ with STEEN Solution™, is part of that evolving innovation in technology.

Organ donation and lung transplantation are each closely regulated. Lung transplantation is a highly specialized field of treatment, and is the only remedy, for patients with end stage lung disease. In the U.S. there are approximately 60 medical centers that perform lung transplants, with one to five surgeons certified to transplant per center. The majority of lung transplant surgeons are trained at a small number of acclaimed centers leading to a fairly homogeneous standard of practice. Six US centers, or approximately 10% of all U.S. centers, that in 2012 performed 304 (17%) of the (1753) US lung transplants[1], participated in the NOVEL clinical trial, leading up to this HDE application.

3.1 Waitlist and Organ Allocation in the U.S.

In 2012 in the United States, 1756 patients with end stage lung disease were transplanted and, on average, approximately 1600 patients were on the waiting list. The statistics also show that on average, 64% of the candidates underwent transplant within 1 year from listing. During 2012, 196 patients were removed from the waitlist because they became too sick to transplant, and 225 patients died waiting for a lung transplant.[1]. This means that more than 25% of the patients died without the chance of a potentially lifesaving therapy. The reason for the insufficient number of lung transplantations made is the limitation in organ availability.

In 2012, lungs had the lowest number of organs transplanted in comparison to livers, hearts and kidneys. The main reason is due to pulmonary consequences of brain death and incidence of smoking related lung diseases in the donor. This has lead to patients who die waiting for an organ to become available. A patient in need of a kidney can receive dialysis or in need of a heart transplant can receive a ventricular assist device while waiting for an organ to become available. A patient waiting for a lung transplant has no such options. Below Table 3 provides a listing of the number of donors and transplants done for each major organ in 2012.

	Kidney	**Liver**	**Heart**	**Lung**
# of Donors in 2012	13,040	6876	2451	1710
# of Transplant in 2012	16,487	6256	2378	1756

Table 3 Comparison of 2012 between Kidney, Liver, Heart, and Lung Total Transplants

The waitlist management and organ allocation process are conducted according to the provisions of the National Organ Transplant Act (NOTA), which became law in 1984. The waitlist and organ allocation process are regulated by the U.S. Department of Health and Human Services (HHS) Health Resources and Services Administration (HRSA), which has developed, and continues to update, detailed and stringent guidelines for assigning patients to waitlists and allocating available donor organs.[2] The National Organ Transplant Act also established the Organ Procurement and Transplantation Network (OPTN) to maintain a national registry for organ allocation. According to NOTA, the OPTN is responsible to increase, and ensure the effectiveness, efficiency and equity of, organ sharing in the national system of organ allocation. Furthermore, the OPTN is responsible for increasing the supply of donated organs available for transplantation. The OPTN awarded responsibility to the non-profit organization United Network for Organ Sharing (UNOS) in 1986. UNOS has since continued to be the sole organization to operate the OPTN. UNOS developed a centralized computer network, UNet, as the national registry for organ allocation: UNet links all transplant centers and organ procurement organizations (OPO), and is staffed 24 hours per day, 365 days per year.   OPOs are regional nonprofit entities that also operate under federal contract and they are responsible for coordinating the donation process when donors become available. There are 58 OPOs in the United States within 11 donor regions.[3]

3.1.1 Waitlist Process

In the U.S., patients requiring lung transplants are assigned to the UNet waitlist registry,[4] based on the Lung Allocation Score (LAS).   The LAS is derived from waitlist urgency (number of days an individual is expected to live in the next year on the waitlist) and post-transplant survival (the number of days an individual is expected to live within the first year post transplant). The higher score the higher the priority to be considered for a donor lung. If the LAS score becomes excessively high, a patient may be removed from the waitlist because their chance of survival after transplant has become too small.

3.1.2 Organ Allocation Process

OPOs evaluate the potential donors, check the deceased state donor registry, discuss donation with family members, contact the OPTN and run a match list, and arrange for the recovery and transport of donated organs.   Upon determining donor designation and death declaration, the OPO assumes responsibility for the care of the donor. The OPO is responsible for notifying the regional transplant centers of the availability of a donor lung(s) by way of UNet. The transplant centers in the OPO regions are offered the donor lung(s) based on blood type, size of donor, and LAS of the patients on the waitlist at each specific transplant center.

The lung allocation process is based on distance from donor location. First zone is within 500 miles of the zip code of the physical location of the donor, and then increasing in 500 mile increments. Transplant centers receive preliminary information concerning the characteristics of the donor and specific organ (e.g. x-ray, pO2, blood group, size). The transplant center can accept or decline the offer based on it not matching a recipient or the quality of the organ or other reasons. If the center with the first patient on the waiting list declines the offer then it goes to the second patient on the list. This continues until the donor lung is placed or the OPO determines it is no longer able to place the organ.

Although a lung donor score (LDS) based on variables from the Australian[5] and European donor databases have been developed, there are no studies adequately correlating them to outcomes post-transplant. In the U.S., therefore, lung transplant centers do not use these scores to accept or reject donor lungs for transplant. At present, the decision to accept a particular donor is up to the individual surgeon, who takes into account donor and recipient factors, but not the LDS score.

The donor lung declines rapidly in comparison to other donor organs. Currently, only 18-20% of donated lungs meet the surgeon's criteria and are transplanted. The remaining lungs that are not considered suitable for transplant are used for laboratory research or discarded.

During the steps required prior to organ procurement, the potential donor patient is maintained on a ventilator. The length of ventilator time increases the risk of lung deterioration due to increased risk of aspiration, edema and infection. To keep the abdominal organs suitable for transplant, blood pressure must be maintained via pharmaceuticals and large boluses of fluid. These pharmaceuticals and boluses of fluid may cause the lungs to deteriorate and cause a decrease in oxygen exchange. In comparison to other organs, the lungs are very susceptible to fluid overload during donor management.

3.2 The International Society of Heart and Lung Transplant (ISHLT) criteria for organ assessment

The International Society of Heart and Lung Transplant (ISHLT) is comprised of Physicians, Researchers, and Nurses with over 2500 members from over 45 countries, representing over 14 different disciplines involved in the management and treatment of end-state heart and lung disease. In all essence, ISHLT consists of members from all lung and heart transplant centers in the world. The ISHLT engages in the regular development of guidelines, consensus documents, standards statements, and policy statements regarding end-stage heart disease, end-stage lung disease, heart transplantation, and lung transplantation.[6] The ISHLT criteria are used to assess the suitability of a donor lung for transplant. The ISHLT publishes official donor and recipient data including survival statistics on all lung transplants that occur worldwide.

3.3 Standard Practice: Organ Procurement and Assessment

Current standard of care provides for the onsite surgeon to evaluate the quality of the donor lung(s) by reviewing the chest x-ray, bronchoscopy, gas exchange, visual inspection, and palpation findings.

Once a lung is accepted and procured, it is flushed with a cold preservation solution (usually Perfadex®), packaged according to standard of practice, and transported in a hypothermic state (~4-10°C) on ice to the center for transplant. The process is done to slow down metabolism to a minimum to conserve oxygen and nutrients and to slow down accumulation of potentially harmful metabolites.

Under current standard practice, the donor lung is brought back to the recipient operating room, and undergoes a final assessment for transplant suitability by the transplant team – often referred to as a "back table assessment" – immediately prior to a scheduled transplant. This "back table assessment" is carried out by visual and palpation assessment for blood clots, contusions, edema and other physically identifiable issues with the donor lung(s).

3.4 Organ Assessment with EVLP

The availability of the STEEN Solution™ with the XPS™ System provides for donor lungs that fail to meet the surgeon's criteria to be reconsidered for transplant following ex-vivo lung perfusion (EVLP). These lungs can be brought to a transplant center with access to the XPS™ System with STEEN Solution™, the EVLP protocol can be initiated, and the donor lung can be re-assessed by the transplant team. Instead of relying on only an overall physical inspection the team can now also assess a lungs functional ability possibly increasing the number of donor lungs transplanted.

The use of the XPS™ with Steen solution™ holds the potential to increase the percentage used of lungs from the donor pool by giving the surgeon additional time and information for evaluating the suitability of the lungs for transplantation. The perfusion at normothermic conditions and the addition of oxygen and glucose normalize the rate of metabolism.

Furthermore, normothermic perfusion permits a more thorough cleanse of remaining intact or broken blood cells and potentially pro-inflammatory blood components like coagulation factors and cytokines as seen in Table 4.

Time Period	EVLP Lung	Standard Lung
Prior to donor lung explant	• Donor blood type • Donor lung size • Visual inspection to assess contusions • Chest x-ray to assess infiltrates • Bronchoscopy to assess secretions	• Same assessments as the EVLP Lung.
Donor Lung Transportation	• Hypothermic transportation - Flushed with Perfadex and placed on ice. • Start of first Ischemic time.	• Transportation is the same as the EVLP lung. • Start of Ischemic time.
Receipt of Donor Lung by Transplanting Center	• End of Ischemic time. • Placed on XPS machine for normothermic EVLP with Steen Solution until ready for transplant. • Re-establishes metabolism permitting oxygen and nutrient exchange, flushing any residual donor blood product.	• Maintained on ice until ready for implant • Ischemic time ongoing.
Prior to Transplant into the Recipient	• Re-evaluated by Physical inspection, x-rays(s), and the XPS System. • Pulmonary Vascular Resistance • Pulmonary Artery Pressures • Left Atrial Pressures • Compliance • PaO2/FiO2 • Placed on ice prior to transplant. Start of second ishemic time.	• Re-evaluated by Physical inspection via the "back table assessment". • Ischemic time ends.
Recipient Transplant	• Transplanted per institutional protocol	• Same as EVLP Lung

Table 4 Comparison between EVLP and Standard lung Process

4 Clinical Data

The sponsor has supported two clinical studies of STEEN Solution™ with EVLP with the FDA being consulted on both protocol designs. The first in Canada, titled the Normothermic Ex vivo Lung Perfusion (EVLP) for an Improved Assessment of Donor Lungs for Transplantation (HELP Study) was a prospective, non-randomized, single-center study conducted at Toronto General Hospital from 2008 to 2010. In this study, STEEN Solution™ was used with off the shelf devices to perform EVLP on lungs initially considered non-acceptable for transplantation. The second study in the U.S. titled "Normothermic Ex Vivo Lung Perfusion (EVLP) as an assessment of extended/marginal donor lungs" (NOVEL trial), was a prospective, non-randomized, controlled clinical trial conducted at six major transplant centers in the US. In this study, STEEN Solution™ was used with the XPS™ (the XPS™ comprises off the shelf devices) to perform the EVLP. The NOVEL trial was initiated in 2011 with a calculated total enrollment of 42-42. This HDE application includes the data from the first 31-31 patients. The study remains open to enrollment under FDA approval for treatment continuation. XVIVO has made a comparison of the HELP off the shelf devices with the XPS system located under Appendix III. Results from the HELP study is listed under Appendix IV HELP Clinical Study Report and results from NOVEL and HELP are listed under Appendix VI Summary of Safety and Probable Benefit.

Appendix III HELP Off the Shelf Devices vs. XPS System

Appendix IV HELP Clinical Study Report

Appendix VI NOVEL Trial Summary of Safety and Probable Benefit

5 Canadian HELP Study

The HELP study was designed as a single treatment arm trial to review clinical outcomes between initially rejected donor lungs treated with 4 hours of EVLP using STEEN Solution™ and conventional transplants during the same time period at the same center. The study was initially approved to enroll 22 patients. The first 3 patients were part of a safety pilot, where standard criteria bilateral lungs were transplanted following EVLP with STEEN Solution™ (one lung was placed onto EVLP while the first lung was being transplanted). Nineteen patients followed this pilot and received lungs initially rejected because of quality (not acceptable for transplantation) but that were deemed transplantable after EVLP with STEEN Solution™. Health Canada permitted expanded access use while the product was under review, resulting in an additional 39 EVLP transplants. Therefore, total study enrollment was 61 patients. STEEN Solution™ received clearance by Health Canada on November 6th, 2012.

The results of the HELP Study were published in 2011 in the New England Journal of Medicine[7]. The NEJM analysis included 20 EVLP transplanted patients (whose lungs initially were determined not to be transplant suitable). Although the HELP Study protocol called for 19 patients, enrollment continued for several more patients. The NEJM analysis included one of these additional patients and the original 19 patients, for a total 20 patients. The data presented below is on the same 20 patients included in the NEJM analysis, but does not include the initial three "normal" lungs that were placed into the pilot study.

The HELP trial design followed the established, regulated process of organ allocation and waitlist prioritization within the Canadian System. Initially unacceptable lungs were defined as those not meeting the current clinical donor lung criteria based on ISHLT guidelines. A donor lung meeting EVLP criteria proceeds through the EVLP procedure at normothermia using STEEN Solution™ with the off the shelf device components to perfuse the lung in a protected environment. The EVLP procedure occurred for up to 4 hours but could end at 3 hrs if deemed transplant suitable. EVLP could end at 2 hours if the donor lung was considered not transplant acceptable. Every hour physiological parameters were measured and assessed.

The transplant suitability was evaluated during EVLP by the composite of:

- delta PO_2>350mmHg (Oxygenation left atrium – Oxygenation pulmonary artery),
- stable pulmonary vascular resistance (PVR)
- pulmonary artery wedge pressure (pAWp)
- lung compliance (a measure of the ease of expansion of the lungs= C-Stat)

Data was collected on recipients of donor lungs meeting standard criteria transplanted during the same timeframe for comparison.

5.1.1 Study Findings-HELP Study

The donors used in the HELP study had significantly lower in vivo PaO2/FiO2s, abnormal bronchoscopies, positive cultures and tended to have more abnormal Chest X-rays. Prior to the HELP study and EVLP Toronto General Hospital did not perform DCD transplants on a routine basis because it was felt that the lungs were not able to be tested accurately. Once they had access to EVLP they began using DCD lungs as shown by the data in Table 5 below. Difference in total preservation time was due in part to the time the lungs were placed on the EVLP circuit.

HELP Study

Donor, Recipient and Transplantation Characteristics

Variable	EVLP (n=20)	Controls (n=116)	P Value
Donor Characteristics			
Age			0.07
Median	38	45	
Range	16-69	6-79	
Best PaO_2/FiO_2 (mmHg) Median	335	459	0.0001
Range	160-532	267-590	
Abnormal chest X-ray (%)	70%	45%	0.05
Abnormal bronchoscopy (%)	90%	52%	0.001
Smoking history >10 pack/day	20	23	0.78
Positive broncho-alveolar cultures (%)	80%	60%	0.04
Donation after cardiac death (%)	45%	2.5%	0.0001
Age (median years)			0.81
Median	56	56	
Range	28-69	19-73	
Recipient diagnosis – Pulmonary	35%	37%	0.65
Retransplantation (%)	5%	4.3%	0.81
Bilateral transplantation (%)	75%	85%	0.36
Lung Allocation Score			0.33
Median	33	34	
Range	27-78	28-83	
Total Preservation Time (minutes)			0.0001
Median	653	370	
Range	267-1021	163-662	

Table 5 Donor, Recipient and Transplantation Characteristics

HELP Study

Recipient Outcomes after Lung Transplantation

Variable	EVLP (n=20)	Controls (n=116)	P Value
Primary Endpoint			
PGD 2 or 3 at 72h	15%	30.1%	0.11
95% CI	0.0439 - 0.3688	0.2254 - 0.3907	
Secondary Endpoints			
PGD 2 or 3 at ICU	25%	30.3%	0.30
95% CI	0.1081 -	0.2206 -	
PGD 2 or 3 at 24h	15%	36.2%	0.07
95% CI	0.0439 - 0.36885	0.2802 to 0.4528	
PGD 2 or 3 at 48h	30%	35.3%	0.46
95% CI	0.1432 - 0.5213	0.2723 to 0.4440	
ECMO (%)	0%	3.5%	0.37
P/F ratio T0h (mmHg) Median	424	372	0.51
Range	85-538	49-591	
Post-transplantation mechanical	2	2	0.15
Range	1-101	1-43	
Post-transplantation ICU stay (days) Median	4	4	0.68
Range	1-101	1-103	
Post-transplantation hospital stay (days)	23	27	0.39
	7-101	9-156	
Bronchial	5%	4.3%	1
95% CI	0 - 0.2541	0.0160 - 0.0995	
30 Mortality (%) 95% CI	10% 0.0157 to	5.2% 0.0216 to	0.33

Table 6 Recipient Outcomes after Lung Transplantation

PGD scores were assessed at time of ICU arrival (T0) and at 24 and 72 hours post transplant for both groups.

HELP Study-Expanded

Primary Graft Dysfunction: EVLP vs. Control

Toronto General Hospital Patients-PGD						
PGD Grade	**Controls N=103**			**EVLP N=35**		
	T 0hr	**T 24hrs**	**T 72hrs**	**T 0hr**	**T24hrs**	**T72hrs**
1	72 (70%)	55 (57%)	63 (64%)	25 (71%)	28 (80%)	30 (86%)
2	16 (16%)	33 (34%)	24 (24%)	5 (14%)	5 (14%)	4 (11%)
3	15 (15%)	9 (9%)	11 (11%)	5 (14%)	2 (6%)	1 (3%)
No Value Obtained	0	6	5	0	0	0

Table 7 PGD Scores between EVLP and Control *Extubated patients were not given a PGD score. Last Follow up Date – May 24, 2013

Long term survival is assessed in the tables below and to date there is not significant survival difference in the EVLP group compared to the control group.

HELP Study-Long-Term Follow Up-

	EVLP N=78	**Control N=560**	**Significance**
Survival 1 year	85.7%	85.9%	P=0.87 (F)
Survival 2 years	77.3%	78.8%	P=0.78 (F)
Survival 3 years	74.9%	70.9%	P=0.87 (F)
***Survival 5 years**	68.7%	60.4%	P=0.72 (F)
Number of acute rejection episodes per year	N=39 0.54±0.72	N=204 0.47±0.65	P=0.54 (MW)
Highest Predicted FEV1 (only double lungs)	N=35 73.5%±28%	N=220 71.8%±25%	P=0.67 (ST)

Table 8 Long Term Follow Up Does not include bridge to transplant patients. The following statistical tests were used in this analysis: F=Fisher's exact test; MW=Mann-Whitney; ST=Student's T-test.

* FDA has only seen Long Term Follow Up through 3 years via Deficiency Letter Requests the 5 year has not been seen by FDA

HELP Study-Expanded

Kaplan-Meier Survival Curve: EVLP vs. Control

(the strength of this methodology is that it includes all patients regardless of time of transplant)

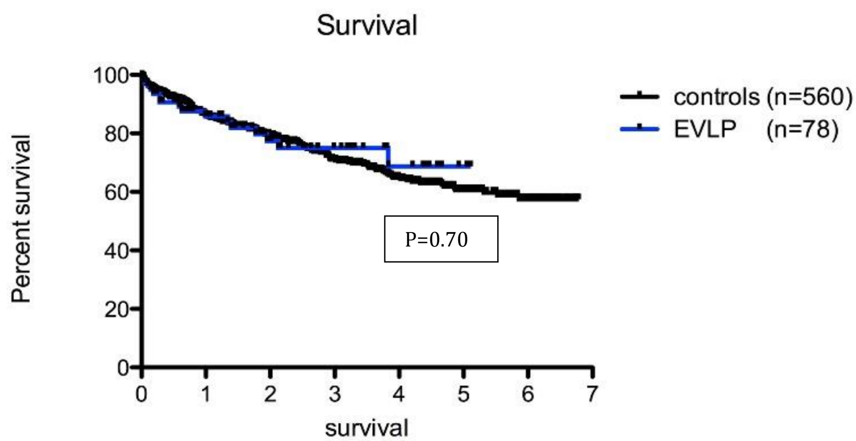


Figure 2 Kaplan Meier Survival Curve

Conclusion: The Kaplan –Meier Survival Curve above shows that long term (5 year) survival is no different for the EVLP (using STEEN Solution™) group compared to all other lung transplant recipients in the Toronto program during the time of the study (= the comparison group).

In an HDE deficiency letter issued on August 8, 2013, the FDA requested PFT data from patient records generated during the Toronto HELP study. The PFT data was not part of the study protocol, but is routinely collected per standard of care. The company complied with FDA's request and provided the retrospective PFT data.

HELP Study-Expanded

Pulmonary Function Tests: EVLP Patients

Toronto General Hospital Patients-PFTs			
PFT Test	**1 Year**	**2 Years**	**3 Years**
FEV1-(Mean)	2.4 (n=39)	2.3 (30)	2.7 (14)
FEV1 (Median)	2.2 (n=39)	2.3 (30)	2.3 (14)
FEV1 % pred (Mean)	72 (n=39)	69 (28)	58 (11)
FEV1%pred (Median)	70 (n=39)	72 (28)	64 (11)
FVC (Mean)	3.2 (n=39)	3.7 (30)	3.3 (13)
FVC (Median)	3.1 (n=39)	3.2 (30)	2.9 (13)
FVC % pred (Mean)	78 (n=39)	81 (28)	71 (11)
FVC % pred (Median)	82 (n=39)	83 (28)	66 (11)

Table 9 HELP Expanded - PFT Results () = number of patients with results. The PFT Data is from N=50 EVLP (20 from the HELP Study)

Lung transplant recipients experience an improvement in pulmonary function after transplant which peaks at 1 year. During this interval a new functional baseline is established for comparison to all future measurements. FEV1, the most common parameter measured and reported, reaches in bilateral lung sets 75% predicted at 1 year and inevitable declines over time and has been reported to be 65% at three years in all comers.

The results of the HELP study indicated that STEEN Solution™ used in an EVLP system is safe, as evidenced by the EVLP recipient group having no significant difference in clinical outcomes compared to those in the Standard recipient control group, and that lung function assessments for EVLP and standard donor lung function post-transplant are similar. Comparison of EVLP and Standard donor lung data shows no clinically significant difference post-transplant between the highest predicted FEV1. (The FEV1 is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity). There was also no clinically significant difference with the number of acute rejection episodes.

Prior to the use of EVLP, Toronto General Hospital used approximately 25% of available donor lungs. After initiating the HELP study and using EVLP lungs, the overall lung utilization rate increased to 36%. This indicates that EVLP with STEEN Solution™ has a probable benefit of safely increasing donor lung usage.

6 U.S. NOVEL Study

6.1 Study Design

Based on findings from the HELP study, the U.S. NOVEL trial was designed as a prospective, multicenter, non-randomized, controlled clinical trial using a very similar protocol as in the Help Study. The purpose was to study the safety of perfusing extended donor lungs with the Steen Solution™ (XVIVO Perfusion, Inc.) with the XPS™ machine prior to transplantation, with the primary purpose of performing a second evaluation to determine acceptability to transplant, with the intent of increasing the donor lung availability. Refer to the Clinical Study Report and the Summary of Safety and Probable Benefit.

Appendix VI Summary of Safety and Probable Benefit

Appendix VII NOVEL Clinical Study Report

6.1.1 Eligibility Criteria: Donor Organs

The NOVEL trial design follows the established, regulated process of organ allocation and waitlist prioritization. Donor lungs were made available for transplant and matched with a recipient at the investigational sites according to federal regulations and OPO policies and procedures. Donor lungs were assessed for transplant suitability according to ISHLT criteria and based on the experience and expertise of the investigator and transplant team.

Donor lungs not meeting standard accepted ISHLT criteria and/or rejected by other transplant centers for 'quality' reasons were eligible for enrollment into the EVLP arm of the study. Neither donor age nor ischemic time was used as a consideration for determination of marginal donor. An EVLP lung undergoes two eligibility assessments: the first is to determine if initially unacceptable lungs meet criteria to go through the EVLP procedure. The second eligibility assessment is post EVLP to determine if the lungs meet transplant suitability.

An initially unacceptable lung is included in the study if it meets the following pre-EVLP inclusion criteria:

- $PaO_2/FiO_2 \leq 300$mmHg
  or
- If $PaO_2/FiO_2 > 300$mmHg with any one or more of the following:
- Multiple blood transfusions.
- Pulmonary edema detected via CXR, bronchoscopy or palpation of lungs.
- Donation after Cardiac Death (DCD).
- Investigator evaluation of donor lung as “unsuitable” for standard criteria for lung transplant. Surgeon must list reason for “unsuitable” determination.

6.1.2 EVLP Procedure

If the donor lung met study eligibility criteria, it was retrieved and flushed with Perfadex® and stored at 4 degrees centigrade per standard lung procurement protocol. The lung was then transported to the study transplant center where EVLP with STEEN Solution™ and the XPS™ machine was initiated. Methylprednisolone, heparin and antibiotics were added to the STEEN Solution which was the same procedure used in the HELP trial.

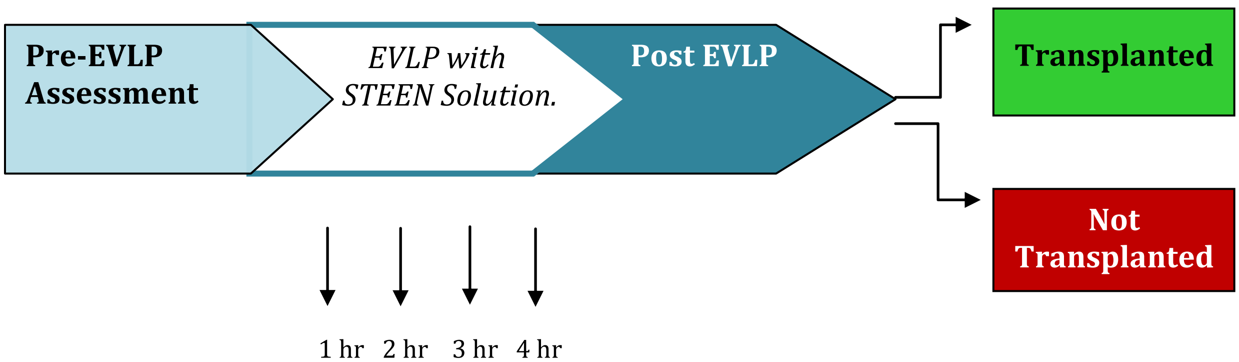
The EVLP procedure, per NOVEL Trial protocol, occurs for up to 4 hours but can end at 3 hrs if deemed transplant suitable. EVLP can end at 2 hours if the donor lung is considered not transplant suitable. Every hour physiological parameters are measured and assessed. An x-ray is performed at 1 and 3 hrs. The determination of transplant suitability is based on the totality of the assessments and the overall trend of improvement. This assessment is not principally different to the initial assessment made in the deceased donor. The physiological parameters measured are as follows:

- Pulmonary Vascular Resistance
- Airway pressures (mAwP, PAwP, platAwP; mean, peak and plateau airway pressures.
- PvO2
- PaO2
- Static Compliance

- Dynamic Compliance (a variable calculated based on the static compliance)

The donor lung is considered transplant suitable based on the delta pO2 (Oxygenation left atrium – Oxygenation pulmonary artery) greater than 350mmHg (this would be an absolute pO2 of ~400 mmHg), stability or improvement during the EVLP procedure of Pulmonary Vascular Resistance (PVR), Compliance, and air way pressure.

A lung could also be excluded if deemed unsuitable based on the clinical judgment of the lung transplant surgeon. **Refer to Appendix XI Instructions for Use.**



Physiological Parameters Assessed

XPS Hemodynamic Monitor

- PVR (Pulmonary Vascular Resistance)
- PAP (Pulmonary Artery Pressure)
- LAP (Left Arterial Pressure)

XPS Hamilton ICU Ventilator

- Peak awP (Peak Airway Pressure)
- Mean awP (Mean Airway Pressure)
- pPlat (peak Plateau)
- cDyn (Dynamic compliance)
- cStat (Static compliance)
- V_T (Tidal Volume)

Blood Gas Machine

- PaO2 (Pulmonary Artery Oxygen)
- PvO2 (Pulmonary Vein Oxygen)

Figure 3 NOVEL Trial - Overview of EVLP

6.1.3 Study Participants

Investigational sites included five US transplant centers: University of Maryland Medical Center; New York Presbyterian Hospital (Columbia Presbyterian); Brigham and Women's Hospital; University of Colorado Medical Center; and Duke University Medical Center. The University of Pennsylvania was later added to the study as the 6th center.

The study protocol provided for a total study enrollment of up to 84 patients, 42 EVLP and 42 Control. The first US study patient was enrolled on August 3rd, 2011. On May 17th, 2013 the 42nd EVLP patient was enrolled and on June 5th, 2013 the 42nd control patient was enrolled. To permit continued access, FDA approved enrollment of an additional 20 patients, 10 in each treatment arm, on May 17th, 2013 and on August 5th, 2013 FDA approved enrollment of an additional 20 patients, 10 in each treatment arm. Data for 62 patients (31 EVLP and 31 Control) are presented in the HDE and its amendments.

6.1.4 Recipient Allocation

Once a lung was determined to be suitable for transplant (ie) no longer considered different in quality than those initially deemed acceptable, it was transplanted into the consented recipient, who had been allocated an organ based on the UNOS system. The research centers concurrently enrolled controls based on the EVLP enrollment to permit enrollment during the same time period, avoiding the possibility of control enrollment completion in a few months and EVLP enrollment completion over the course of several years. The NOVEL trial did not use stratification of diagnosis or lung type (Single or bilateral) between the treatment arms. Therefore attention should be given to differences in recipient diagnosis since this strongly influences morbidity and mortality post transplantation [8]

The FDA requested additional data to determine if the EVLP lungs had been rejected by other centers. This additional request was not part of the study protocol. To comply with FDA's request, the company asked UNOS to provide a match run to determine the recipient placement on the waiting list and if attempts had been made to allocate them to any other centers. This data is shown below:

Lung Match Runs For all Donor Lungs Receiving EVLP and subsequently transplanted

NOVEL Study

UNOS Encrypted Donor ID	Were there Recipient Match Rejections due to 'Poor Lung Quality'*	Recipient Match Sequence **	Recipient Match Attempts by OPO***	Furthest Zone Attempted ****
(b) (6) [redacted]	Yes	38	38	B
[redacted]	Yes	11	35	B
[redacted]	Yes	5	8	B
[redacted]	Yes	1	25	local
[redacted]	Yes	1	41	A
[redacted]	Yes	116	126	B
[redacted]	Yes	39	50	local
[redacted]	Yes	72	84	A
[redacted]	Yes	296	299	B
[redacted]	Yes	3	3	local
[redacted]	Yes	7	7	A
[redacted]	Yes	4	10	A
[redacted]	Yes	44	156	A
[redacted]	Yes	26	75	D
[redacted]	Yes	49	56	A
[redacted]	Yes	49	130	A
[redacted]	Yes	8	16	A
[redacted]	Yes	6	31	A
[redacted]	Yes	2	98	A
[redacted]	Yes	9	17	A
[redacted]	Yes	2	129	A
[redacted]	Yes	7	12	A
[redacted]	Yes	40	44	A
[redacted]	Yes	15	20	local
[redacted]	Yes	32	33	A
[redacted]	Yes	1	4	A
[redacted]	Yes	147	163	A
[redacted]	Yes	104	104	A

Table 10 Recipient Match Sequence

In Table 10, the third column lists the recipients' place on the waiting list for the lung donor offer. The Recipient Match Attempts by OPO lists the number of attempts to place the lung before it was provided to the recipient. For instance, donor ID (b) (6) [redacted] was the first person on the list and should have gotten the lung, but since it was going to go on EVLP, the OPO made 25 more attempts to place the lung without success.

Conclusion: All donor lungs used were previously turned down by multiple other centers prior to receipt at trial center for EVLP.

6.2 Study Findings

6.2.1 Donor Characteristics

The following table shows the donor functional demographics for lungs that were used in both the EVLP group (n=54 all EVLP donors) and the Control group (n=31). Donor lungs for both groups were the same except that the EVLP donor group had statistically significant lower PaO_2s prior to retrieval than the Control group:

NOVEL Study

Donor Characteristics: All EVLP Lungs vs. Control

Donor Data	EVLP (n=54)*	Controls (n=31)	*P*
Age **Median (Range)** **Mean (StDev)**	 **29 (13-65)** **31.2 ± 13.4**	 **37 (19-62)** **36.9 ± 13.1**	 ***0.03***
M/F	**29/25**	**21/10**	***0.26***
BD/DCD	**47/7**	**30/1**	***0.25***
Cause of Death **CVA/Stroke** **Trauma** **Hypoxia/Anoxia**	 **11** **25** **18**	 **10** **11** **10**	 ***0.30*** ***0.37*** ***1.00***
PaO2 in Donor **Median (Range)** **Mean (StDev)**	 **347 (119-501)** **335 ± 91**	 **411 (285-589)** **422 ± 79.2**	 ***0.<0001***
CMV (+)	**22**	**16**	***0.37***
Smoking History	**22**	**13**	***1.00***
BAL (+)	**21**	**15**	***1.0***

Table 11 NOVEL Trial All Donor Characteristics EVLP vs. Control * More lungs were tested than transplanted. This table shows all lungs placed on EVLP.

When the total group of EVLP lungs is divided into those that were eventually transplanted after EVLP and those that were rejected the data table shows that there is no difference in the donor characteristics.

NOVEL Study

Donor Characteristics: EVLP Lungs Transplanted vs. Not Transplanted

Donor Data (in situ, prior to explant)	EVLP Tx (n=29)*	EVLP non-TX (n=25)	*P*
Age Median (Range) Mean (St Dev)	 31 (16-65) 33.5 ± 13.7	 25 (13-48) 28 ± 12.7	 0.17
M/F	17/12	13/12	0.78
BD/DCD	27/2	20/5	0.23
Cause of Death CVA/Stroke Trauma Hypoxia/Anoxia	 3 14 12	 8 11 6	 0.09 0.79 0.25
PaO_2/FiO_2 Median (Range) Mean (St Dev)	 350 (166-500) 319 ± 108	 333 (119-501) 352 ± 73.5	 0.90
CMV (+)	10	12	0.41
Smoking History	13	9	0.59
BAL (+)	12	9	0.52

Table 12 Donor Characteristics EVLP Transplanted vs. not transplanted

Conclusion: These results indicate that there were not statistically significant differences in donor characteristics between transplantable and non-transplantable donor lungs. It was the information gained during EVLP that led to the decision whether or not to transplant each lung.

Lungs are declined for transplant due to a variety of reasons. In general, it is the totality of the donor lung being assessed for transplant and not one specific parameter. Of the 29 EVLP lungs transplanted across 31 recipients (3 splits) 5 met the criteria of PaO2 less than 300 with the other 24 having a PaO2 greater than 300 with other reasons for inclusion being: 2 DCDs, 20 Pulmonary Edema/infiltrates/ Contusions/Drowning/Multiple Blood transfusions, and 1 Asphyxiation (secondary to hanging).

NOVEL Study
Donor Characteristics: EVLP Lungs Transplanted

Donor ID N=29	Lung Type	Age of Donor	PaO2	Reason considered an EVLP Eligible Lung
(b) (6) [redacted]	B	45	350	Drowning, Pulmonary Edema
[redacted]	B	49	337	Infiltrate lower lobe
[redacted]	B	20	375	Contusion
[redacted]	B	30	358	Contusion
[redacted]	B	18	469	Pulmonary Edema, Suspected aspiration
[redacted]	RS	24	362	Pulmonary Edema, Lower Lobe infiltrates
[redacted]	B	36	227	PaO2=227
[redacted]	B	37	423	, Contusions and Consolidations
[redacted]	RS	16	389	Multiple Blood Transfusions
[redacted]	RS	19	346	Radiographic Finding, Palpation
[redacted]	B	53	350	Pulmonary Edema, Poor Compliance
[redacted]	RS	65	166	PaO2=166
[redacted]	LS	60	499	Presence of Contusion on CT.
[redacted]	RS	38	278	PaO2=278, Hanging
[redacted]	LS	31	386	Pulmonary Edema
[redacted]	B	20	500	Asphyxiation
[redacted]	LS	46	256	PaO2=256
[redacted]	LS	50	330	Multiple Blood Transfusions
[redacted]	B	23	311	Pulmonary Edema, Multiple Blood Transfusions
[redacted]	B	24	316	Lower Lobe Edematous, Multiple Blood Transfusions
[redacted]	B	16	390	Pulmonary Edema, Lungs boggy, Multiple Blood Transfusions
[redacted]	RS	29	412	Pulmonary Edema, Lungs boggy
[redacted]	B	39	305	DCD
[redacted]	B	22	420	Pulmonary Edema, Multiple Blood Transfusions
[redacted]	LS	34	349	Pulmonary Edema, Lung Boggy
[redacted]	B	31	348	Pulmonary Edema, Lung Boggy
[redacted]	RS	20	350	Pulmonary Edema, Questionable Aspirations
[redacted]	B	29	286	DCD, PaO2=286, PaO2=256
[redacted]	B	48	324	Pulmonary Edema, Lung Boggy, High peak airway pressure.

Table 13 NOVEL Trial-EVLP Transplanted Reasons Initially Unacceptable

Of the 25 EVLP not transplanted, 10 met the criteria of PaO2 less than 300 with the other 15 having a PaO2 greater than 300. Other reasons the lungs were not transplanted include: 2 DCDs, 11 Pulmonary Edema/Infiltrates/Multiple Blood transfusions, and 2 Infarcts/Unable to Bronchoscope - clots noted on flush.

NOVEL Study

Donor Characteristics: EVLP Lungs Not Transplanted

Donor ID N=25	Lung Type	Donor Age	PaO2	Reason considered an EVLP Eligible Lung
(b) (6) [redacted]	B	24	429	Pulmonary Edema, Infiltrate Lower Lobe, Drowning.
	B	48	389	Pulmonary Edema, Infiltrate Lower Lobe
	B	42	227	PaO2= 227
	B	43	335	Marginal LLL gas (266) Clots noted on retrograde flush; unable to bronch
	B	45	376	Infarcts
	RS	22	482	DCD, Pulmonary Edema, Lower Lobe infiltrate
	B	21	501	Pulmonary Edema, Multiple Blood Transfusions
	LS	48	351	DCD, Pulmonary Edema
	RS	24	332	DCD, Pulmonary Edema
	B	13	218	PaO2=218
	B	19	423	DCD, Asphyxiation
	RS	14	240	PaO2=240
	B	13	333	Pulmonary Edema
	B	13	352	Pulmonary Edema, Lungs boggy
	B	25	390	Pulmonary Edema, Lungs boggy
	RS	46	204	PaO2=204
	LS	29	412	Pulmonary Edema, Lungs boggy
	RS	29	266	DCD, PaO2=266
	LS	28	276	PaO2=276
	B	20	472	Pulmonary Edema, Lungs boggy
	B	13	169	PaO2=169
	B	29	119	PaO2=119
	B	45	310	Pulmonary Edema, Mild atelectasis/infiltration in left lower lobe, Infarct(PE) in Rt.
	B	16	230	PaO2=230
	RS	44	128	PaO2=128

Table 14 NOVEL Trial-EVLP not Transplanted Reasons Initially Unacceptable

Surgeons use the ISHLT as a guideline to assess the lung and decide on whether to use it for transplant.   However, it is a guideline and a clinical decision is made based on their experience, expertise and ultimately what is best for their patient. Either the two main groups surgeons identify as least likely to accept for transplant are lungs with a PaO2 of less than 300 or Donation after Circulatory Death (DCD) donors. In the NOVEL trial 6 lungs had a PaO2 less than 300 or were from a DCD donor. These lungs were transplanted across 7 recipients who all lived past 30 days. The one subject died due to the aortic injury that occurred prior to transplant. The other EVLP lungs transplanted had various reasons such as edema, infiltrates, contusions, multiple blood transfusions.

	Lungs with PaO2 < 300 **N=16**	**DCD** **N=7**
Transplanted	**6****	**2**
Not Transplanted	**10***	**5**
Alive after 30 days	**5**	**2**

Table 15 Comparison of Low PaO2/DCD between EVLP Transplanted Vs. Not Transplanted

*One donor was a DCD with PaO2 less than 300 mmHg.

**DCD donor with differential gases of a PaO2 less than 300 mm Hg for donor (b) (6) [redacted]

When donor characteristics of donor lungs used for transplant after EVLP and those donor lungs used for the control patients there is no difference in the two groups except for the donor paO2/FiO2 is significantly lower in the EVLP group.

NOVEL Study

Donor Characteristics: EVLP Lungs Transplanted vs. Controls

Donor Data	EVLP Tx (n=29)*	Control (n=31)	*P*
Age Median (Range) Mean (StDev)	 31 (16-65) 33.5 ± 13.7	 37 (19-62) 36.9 ± 13.1	 0.33
M/F	17/12	21/10	0.59
BD/DCD	27/2	30/1	0.61
Cause of Death CVA/Stroke Trauma Hypoxia/Anoxia	 3 14 12	 10 11 10	 0.06 0.43 0.59
PaO2 Median (Range) Mean (StDev)	 350 (166-500) 319 ± 108	 411 (285-589) 422 ± 79.2	 <.001
CMV (+)	10	16	0.41
Smoking History	13	13	1.00
BAL (+)	12	15	0.52

Table 16 Donor Lung Characteristics EVLP Transplanted vs. Control

6.2.2 Ex Vivo Evaluation Data

The following table 17 shows that the EVLP lungs that were transplanted had significantly higher pO2's at the end of EVLP than those lungs not transplanted.

NOVEL Study

Donor Lung PO2 Measurements Post-EVLP

	EVLP-TX (n=31)	EVLP Not TX (n=25)	P
Best PO2 Median (range) Mean (StDev)	514 (351-660) 508$\pm$ 71	386 (121-650) 394 $\pm$ 122	**<.001**
Delta PO2 Median (range) Mean (StDev)	401 (221-595) 400 $\pm$ 88	268 (14.5-594) 283 $\pm$ 127	**<.001**

Table 17 Donor Lung PO2 Measurements Post EVLP

Table 18 below shows that the pulmonary artery pressures, left atrial pressures and the pulmonary vascular resistance, although valuable information, was not a deciding factor in determining if the lung was transplantable. What was indicative of a transplantable lung was the combination of the compliance (C-Stat information obtained from the XPS™ ventilator) and the pO2.

NOVEL Study

Key Parameters at time of Decision to transplant or reject lungs after EVLP

Group	N	PA (mmHg) Median	LAP (mmHg) Median	PVR (mmHg) Median	C-Stat (dynes) Median	pO2 (mmHg) Median
EVLP Transplanted	29	10	4	279	107.5	500
EVLP Rejected	25	10	4	298	71	364
P Value		0.86	0.58	0.29	**.006**	**0.0001**

Table 18 EVLP Transplanted vs. Not Transplanted Key Parameters

Conclusion: The results indicate that PO_2 in combination with the compliance of the lung are the major parameters used during EVLP to determine acceptability for transplantation.

6.2.3 Ischemic Time

Total Ischemic time is normally defined as the time from cold flush in the donor to release of the clamps in the recipient at time of transplant. Retrospective review of UNOS data of 6,055 transplants revealed no increased incidence of BOS or 3 year mortality in recipients with local, regional or national lung donors despite national ischemic times of 342 minutes +/-90 [35]. Additional single center studies verify no change in survival for ischemia greater than 6 hours [36-40]. Donor ischemia time > 7 hours and donor age > 50 years compounded, however, was associated with decreased recipient survival at 2 years [41].

The ischemic time (hypothermic state) in the NOVEL Study is measured at two time points. The first time is the time from cross-clamp/cold flush until the start of EVLP (Ischemic Pre EVLP). The second time point is the end of EVLP until time of transplant (Ischemic Post EVLP). The control arm ischemic time is measured as the time of cross clamp/cold flush until time of transplant (Control). The figure below shows that there is a similar ischemic time in the control versus each of the two time periods for the EVLP group. The EVLP with STEEN Solution, is at normal body temperature which normalizes the rate of metabolism and since the lungs are also ventilated this permits oxygenation, as measured periodically during EVLP. STEEN solution contains glucose which is needed for this normal metabolism. Therefore the time on EVLP is not included in the ischemic time (Ischemia is defined as restriction in delivery of oxygen and glucose needed for normal metabolism).

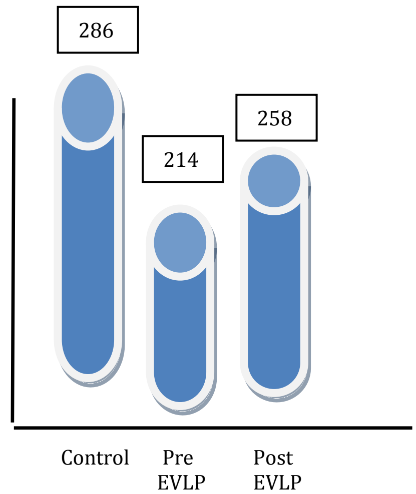


Figure 4 Ischemic Time Between Control and EVLP Lungs

NOVEL Study

Ischemic Time: EVLP vs. Control

<table>
<tr><th>Time Period</th><th>EVLP Tx (n=31)</th><th>Control (n=31)</th></tr>
<tr><td>1st Ischemic Time in
Minutes
Median (range)
Mean (StDev)</td><td>
214 (70-352)
204 ± 74</td><td rowspan="3">286 (114-602)
306 ± 114</td></tr>
<tr><td colspan="2">EVLP (lung is given oxygen and nutrients)
Median time 220 minutes</td></tr>
<tr><td>2nd Ischemic Time in
Minutes
2nd lung implant
Median (range)
Mean (StDev)</td><td>

258 (56-517)
271 ± 125</td></tr>
</table>

Table 19 Ischemic Time between EVLP vs. Control

The table 19 above indicates that you can extend the time outside the body (median time outside the body of 692 minutes EVLP group/ 286 minutes control group)with the use of EVLP as both groups of patients appear to have performed equally well after lung transplantation as the results in the data below reveal.

6.2.4 Recipient Characteristics

A total of 54 donor lungs received EVLP. Twenty-nine lungs were transplanted and 25 were not transplantable. Some bilateral lungs were tested then split and placed into two single-lung recipients. Therefore, 29 donors became 31 recipients. There is no significant difference in demographics between lungs undergoing EVLP versus lungs transplanted in the control group. In the NOVEL trial, investigators evaluated more organs than they would have if EVLP were not available, including DCD lungs.

Recipient demographics (EVLP n=31 and Control n=31) include the primary diagnosis, the presence of cytomegalovirus, and the Lung Allocation Score (LAS) at the time of transplant. All subjects EVLP n=31 Control n= 31 met eligibility to enroll. The NOVEL trial was non-randomized and non-stratified leading to a higher LAS score in the EVLP arm and a higher rate of Idiopathic Pulmonary Fibrosis [8,10](IPF) Lung diagnosis. The IPF diagnosis has one of the highest rates of mortality/morbidity post transplantation compared to other diagnosis groups[8]. The higher rate of IPF in the EVLP treatment arm was due to the study design and the adherence to the standard organ allocation process and matching of the recipients.

NOVEL Study
Recipient Characteristics: EVLP vs. Controls

Recipient Data	EVLP (n=31)	Control (n=31)	*P*
Age Median(Range)	63 (31-77)	59 (37-72)	0.14
M/F	20/11	16/15	0.44
Single/Bilateral	16/15	12/19	0.44
Diagnosis			
IPF	**17**	**8**	**0.03**
COPD/Emphysema	11	13	0.79
PPH	1	3	0.61
Cystic Fibrosis	1	3	0.61
Bronchiectasis	1	0	1
Scleroderma	0	1	1
A1T1	0	2	1
LAM	0	1	1
CMV (+)	18	14	0.44
LAS Score Median (Range)	**40** (31-95)	**37** (28-72)	0.18

Table 20 Recipient Characteristics EVLP vs. Control

Conclusion Among the recipients of lungs selected with the help of EVLP, the IPF diagnosis was the only diagnosis where there was a statistically significant difference. This is an important finding, because mortality is generally higher in patients with IPF and such patients generally achieve their maximal lung function more slowly post transplantation than patients with other diagnoses.

6.2.5 Primary Outcome Measurement

The primary endpoint of the NOVEL trial was a 30 day survival comparison between both the EVLP and Control arms. Survival in both the EVLP and Control arms is similar to the combined International lung transplant data available from ISHLT Registry:

NOVEL Study
Primary Outcome Measurement: 30 Day Survival
EVLP vs. Controls

Group	30 Day Patient Survival (Primary Protocol Outcome Measurement	90 Day Patient Survival
EVLP Transplant (n=31)	97%	97%
Control Transplant (n=31)	100%	100%
ISHLT Registry Reference*	94%	88%

Table 21 Thirty-Day Survival EVLP vs. Control *Thirty day survival, as reported by the International Society for Heart and Lung Transplant (ISHLT) Registry, is 94% for all lung transplants in their registry database[6]. The overall 30 day survival for NOVEL Trial lung recipients receiving a lung transplant after EVLP was 97%.

The FDA has raised concerns that 30 day mortality is too short a timeframe to identify mortality in correlation to the implanted organ. Therefore 90 day mortality has been reviewed, and determined to be exactly the same as the 30 day concluding that 30 day time point is relevant in identifying mortality related to the implanted organ. There was no death in the control group and one death in EVLP group during the primary outcome measurement period. This death was determined to be related to reperfusion injury due to Cytokine Release Syndrome and was adjudicated by the safety committee to be unrelated to the EVLP.

The Kaplan Meier Curve below shows that when the 31 recipients that have received EVLP lungs are compared to the 31 control recipients in the study, there is no statistically significant difference between the groups. These two groups are shown in the Kaplan Meier Survival Curve below. ISHLT Registry survival data for recent transplant years have shown survival to be 1 year-81%, 2 yr -73% and 3 yrs survival -66%.

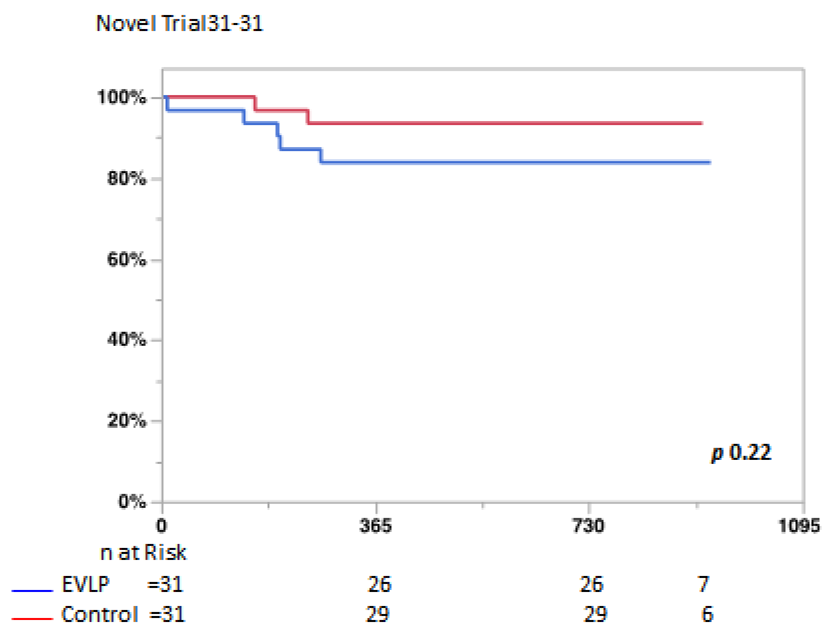


Figure 5 Thirty Day Survival Kaplan Meier Curve

6.2.6 Secondary Outcome Measurements

The NOVEL study protocol identified the following post-transplant findings as secondary outcome measurements:

- Primary Graft Dysfunction (PGD) at 24 and 72 hours;
- Requirments for Extracorporeal Life Support (ECLS/ ECMO);
- Mechanical ventilation days;
- ICU stay days; Hospital stay days; and
- 1 year survival status.

There are no statisitically significant differences between the EVLP and control study arms for any of the secondary outcome measurements. ISHLT reference data has also been provided to provide additional perspective to study findings.

NOVEL Study

Secondary Outcome Measurements: EVLP vs. Control vs. ISHLT

Lung Tx Outcomes	ISHLT Reference Data	EVLP Tx (n=31)	Control (n=31)	***p***
PGD (Primary Graft Dysfunction)	18%	8 (26%)	5 (16%)	0.53
24 hrs	28%	5 (16%)	2 (6%)	0.42
2				
3	11%	3 (10%)	4 (13%)	1
72 hrs	18%	3 (10%)	1 (3%)	0.61
2				
3				
PGD (adjusted)**				
24 hrs				
2	18%	8 (26%)	5 (16%)	0.53
3	28%	3** (10%)	2 (6%)	0.67
72 hrs				
2	11%	3 (10%)	4 (13%)	1
3	18%	1** (3%)	1 (3%)	0.48
Patients ECLS post Tx # Days	n/a	2* (6%) 5	1 (3%) 4	1
Mech Ventilation Days Median (Range)	n/a	1 (1-196)	1 (1-29)	0.49
ICU Stay Days Median (Range)	n/a	4 (1-197)	3 (1-144)	0.68
Hospital Stay Days Median (Range)	n/a	13 (4-198)	11 (6-236)	0.13

Table 22 EVLP vs. Control vs. ISHLT Secondary Outcomes

*Note: one control and two EVLP recipients were placed on ECLS prior to implant of donor lung due to pressure issues and although they were scored as having PGD 3 at 24 and 72 hours

(due to the definition of PGD) this score does not represent their graft status post-transplant. Therefore, these patients have been excluded from the adjusted analysis.
ECLS=Extended Cardiac Life Support (i.e. ECMO)

NOVEL Study

12 mos. Survival: EVLP vs. Control (31:31) vs. ISHLT

Lung Tx Outcomes	ISHLT Reference Data	EVLP Tx (n=31)	Control (n=31)	***p***
1 Year Survival % (IPF and Non-IPF Combined)	81%	87%	94%	0.43
1 Year Survival % (IPF Only)	74%	N=17 76%	N=8 74%	1.0
1 Year Survival % (IPF Excluded)	N.A.	N=14 93%	N=23 100%	.38

Table 23 Twelve Mos Survival EVLP vs. Control vs. ISHLT

6.2.7 Mortality after primary outcome measurement period

Seven deaths occurred in the study. All five EVLP deaths were determined to be unrelated to the EVLP procedure both by the investigators and by the safety review committee. Of note is the fact that five deaths occurred in recipients with a primary lung diagnosis of idiopathic lung fibrosis[8,10] (IPF), which has a greater risk of mortality post-transplant.

NOVEL Study
Mortality Summary: EVLP vs. Control

Subject ID	Tx Arm	Donor Type	Recipient Dx	PGD at 72 Hrs	LAS	Hospital Stay (Days)	Survival (Days)	Cause
(b) (6) [redacted]	Control	BD	IPF	0	47	10	160	Airway Stenosis Respiratory Failure
[redacted]	Control	BD	IPF	2	39	250	250	Renal Failure
[redacted]	EVLP	BD	IPF	3	32	10	10	Reperfusion injury due to Cytokine Release Syndrome
[redacted]	EVLP	BD	IPF	2*	49	13	141	Acute Rejection Respiratory Failure
[redacted]	EVLP	DCD	IPF	3	43	198	198	Complication s from Aortic Injury
[redacted]	EVLP	BD	IPF	1	71	67	203	Airway Stenosis Respiratory Failure
[redacted]	EVLP	BD	COPD	0	33	13	272	Bronchiolitis Obliterans Syndrome

Table 24 Deaths

Appendix V Death Narrative Reports per Subjects

The actuarial survival curve shown below in Figure 6 consists of only the IPF patients in both the EVLP and the Control groups. These survival curves are shown against the survival of IPF patients from the ISHLT Registry as a reference point.

NOVEL Study

Kaplan-Meier Survival Curve

Survival for IPF Recipient

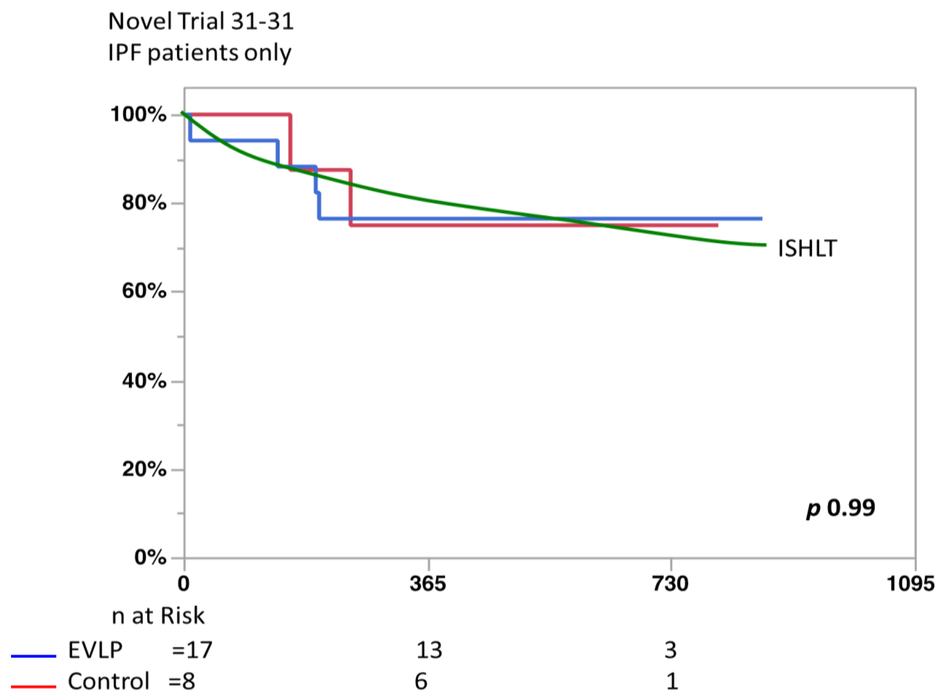


Figure 6 Kaplan-Meier IPF Survival Curve

6.2.8 PFT Data

Pulmonary function tests (PFT) were not part of the protocol, but were collected retrospectively at the request of the FDA, and are listed in the table below. The PFTs are performed on all patients as standard of care post-transplant. However, because it was not part of the protocol, the PFT data was not necessarily collected at all time points among all patients and at all centers. The data below represent the available data points for FDA's retrospective data request. Note that the EVLP group has a higher percentage of patients with IPF and patients who underwent single lung transplant. These patients will have lower PFT values. Additionally, IPF patients will take longer for their chests to remodel, resulting in longer times to reach maximal improvement in lung function[8,10].

Pulmonary Function Tests										
	1 mos. FEV1% pred.	1 mos. FVC% pred.	3mos FEV1% pred	3mos. FVC% pred	6mos FEV1 % pred	6mos FVC % pred	9 mos FEV1 % pred	9mos FVC % pred	12 mos. FEV1 % pred	12 mos. FVC % pred
EVLP	63	60	69	66	69	73	65	71	64	68
Controls	70	66	73	75	64	72	75	81	88	83

Table 25 All Subjects PFT Data * Patients are not divided by singles/bilaterals or by diagnosis.

6.3 Adverse Events

Adverse events were collected on an ongoing basis for the first 12 months post-transplant. The Primary Investigators or Co-Investigators at each site determined the rating of severity and causality.

An independent safety monitor reviewed each of the serious adverse events (SAEs) reported during the course of the NOVEL study. A safety committee appointed for purposes of the study also reviewed SAE's. All of the reported adverse events summarized below were deemed unrelated to the EVLP procedure and consistent with anticipated adverse events for patients undergoing lung transplant, which include:

- Death
- Renal failure or dysfunction
- Respiratory dysfunction/Infection
- Primary Graft Dysfunction
- Acute rejection
- Cardiac Arrhythmias
- Bronchiolitis Obliterans Syndrome (BOS)/ CLAD
- Bronchiole Stenosis/Dehiscence

In addition, risks due to the implantation on procedure or anesthesia may also occur.

The subjects received standard of care bronchoscopy with the protocol requiring specific findings as reportable such as clinically significant dehiscence, A2B2 rejection, stenosis, and bronchial infections treated with antibiotics. Any other bronchial disorders could also be reported under the "other" category. The EVLP and control arms did not experience any incidences of dehiscence, four EVLP subjects experienced stenosis three have recovered. EVLP Subject [redacted] who died seven months after transplant sustained an aortic injury prior to the lung transplant leading to a cascade of events such as sepsis, pneumonia, PGD grade 3, acute rejection, bronchial stenosis and skin infections. The control arm had two subjects with stenosis one who recovered and the other who died five months post transplant.

It is expected in this study population post transplant to have positive BALs, dyspnea, pneumonia, gastric reflux, electrolyte imbalance, pneumothorax post bronchoscopy, and skin or hospital acquired infections. The types of events reported are consistent within this study population. In addition, complications due to the procedure can lead to post operative complications. In reviewing the events between the two treatment arms there was no clinical significant difference between the two arms. Some EVLP subjects had post operative complications due to the surgical procedure (ie) Aortic injury.

In order to review a summary of the events the terms were listed under a system organ class. Cardiac disorders classify the different type of arrhythmias and heart failure. The vascular disorders capture ischemic injury, pulmonary emboli, (DVT) thrombosis, hypertension, and cardiac arrest. Acute rejection is reported via the bronchial AEs if at a grade A2B2 and all other episodes have been listed in a table at the request of the FDA. Some centers also reported rejection as an AE which has been listed under immune system disorders. Primary graft dysfunction is being reported at 0, 24, and 72 hrs and has also by some sites been reported as an AE and is listed under injury, poisoning, and procedural complications. Under this system organ class are also any post operative complications (ie) hematoma, delay wound closure.

The infections and infestations system organ class includes skin infections, nosocomial infections, upper respiratory viral infections, ear, nose and throat infections. All pneumonia (viral and/or bacterial) are reported under the respiratory, thoracic and mediastinal disorders. If the pneumonia had a positive culture it was not also reported under the infection system organ class.

	EVLP	Control
TOTAL # Patients per Arm	31	31
TOTAL # Patients with Incidence	27	22

		EVLP					Control				
AE System Organ Class		# of Patients	# of Incidence	Number of Device Related Incidences	Serious EVLP	Non-Serious EVLP	# of Patients	# of Incidence	Number of Device Related Incidences	Serious Control	Non-Serious Control
Cardiac Disorders		1	2	0	0	2	2	2	0	1	1
Eye Disorders		0	0	0	0	0	1	1	0	0	1
Gastrointestinal Disorders		4	5	0	1	4	6	6	0	4	2
General systems disorder		0	0	0	0	0	1	1	0	1	0
Immune system disorders		5	5	0	4	1	3	5	0	5	0
Non Respiratory Infections and infestations											
Non Respiratory Infections and infestations Sub-Class*	Fungal Infection	1	1	0	0	1	0	0	0	0	0
	Viral Infection/CMV	2	3	0	3	0	0	0	0	0	0
	Bacterial infection	4	4	0	2	2	0	0	0	0	0
	Infection Other	0	0	0	0	0	2	2	0	2	0
Injury, Poisoning, and procedural complications		5	6	0	5	1	4	7	0	6	1
Metabolism and nutrition disorders		1	1	0	1	0	4	3	0	2	1
Musculoskeletal and connective tissue disorders		3	3	0	2	1	1	1	0	1	0
Nervous System Disorders		1	1	0	0	1	0	0	0	0	0
Psychiatric Disorders		1	1	0	1	0	2	2	0	1	1
Renal and urinary disorders		4	4	0	2	2	2	3	0	2	1
Respiratory, thoracic and mediastinal disorders											
Respiratory, thoracic and mediastinal disorders **Sub-Class***	Pneumonia	4	4	0	4	0	3	3	0	3	0
	Pneumothorax/ Hemothorax/ Hydropneumothorax	8	8	0	5	3	2	3	0	2	1
	Dyspnea/Respiratory Distress	5	6	0	6	0	8	11	0	11	0
	Pleural Effusion/ Pseudomembran	4	5	0	5	0	3	3	0	1	2
	Chest Pain	1	1	0	0	1	0	0	0	0	0
	Other	4	4	0	1	3	1	1	0	1	0
Skin and subcutaneous tissue disorders		2	2	0	0	2	1	1	0	1	0
Vascular disorders		8	8	0	2	6	3	3	0	2	1
Blood and Lymphatic System		1	1	0	1	0	0	0	0	0	0
Surgical and medical procedures		1	1	0	1	0	0	0	0	0	0
Endocrine disorders		0	0	0	0	0	1	1	0	1	0
Hepatobiliary		1	1	0	0	1	0	0	0	0	0
TOTAL		N/A	82	0	52	31	N/A	54	0	42	12

Table 9 Adverse Event Table. Patients may have multiple types of Infection or Respiratory Disorder within Sub-Class.

Patients post lung transplant have a significant number of bronchoscopies performed in order to monitor their lung status. Some centers perform these routinely and others perform them when the patient's symptoms require more information to be obtained. Although the NOVEL protocol required the clinically significant dehiscence, clinically significant stenosis, A2B2 rejection, and infection treated with a systemic antibiotic to be reported as an AE the FDA later requested further information on all results of all bronchoscopies performed and the following information in the table (Table 28) below was obtained from all centers.

Rejection Biopsy Results		
	EVLP	**Control**
Total # Subjects Reviewed	31	31
Total # Subjects With TBB	29	30
Total Number of TBB Completed	154	157
Total # Bronchs without TBB	17	14
Total # Biopsy Resulting in A0	112	113
Total # Biopsy Resulting in A1	23	30
Total # Biopsy Resulting in A2	11	9
Total # Biopsy Resulting in AX	7	4
Total # Biopsy Resulting in B0	79	92
Total # Biopsy Resulting in B1	4	4
Total # Biopsy Resulting in B2	2	0
Total # Biopsy Resulting in BX	52	40
Total # Biopsy Resulting in R	3	3
Number of Patients with A2 or B2 Rejection	10	5
Number Patients with A2 or B2 Rejection Resolved	8	3
Number of Patients with A2 or B2 Rejection Ongoing	2 (A2B1R now A0B1R) (A2 now A1)	2 (A2 now A1) (A2B0 now A2B0)

Abbreviation	Definition
TBB	Transbronchial Biopsy
A	Acute Rejection
A0	None
A1	Minimal
A2	Mild
A3	Moderate
A4	Severe
X	Ungradeable (not enough tissue)
B	Airway Inflammation (Bronchioles Only)

Table 28 All Recipients Bronch Data

Almost all lung transplant recipients experience rejection at some time post-transplant. The ISHLT registry indicates that acute rejection affects up to 55% of lung transplant recipients within the first year after transplant. There was no difference in the number of bronchoscopies performed nor in the number of rejection episodes that were seen in the two groups of recipients and all of the 31 patients are at one year post-transplant.

After the first 30 days the most common causes of death result from infection and rejection. [9] During the course of follow-up, we have identified no difference in the rate of rejection between EVLP and controls (Table 28). Respiratory infection was identified in 4 EVLP recipients and 3 controls. In all (or almost all) cases the infection was treated and resulted in similar mortality between groups (Figure 5).

7 Summary of Risks and Probable Benefit

7.1 Risks

The safety profile of EVLP with STEEN Solution™ for donor lungs and recipients is very favorable. The XPS™ with STEEN solution™ has shown it does not damage lungs and the system did not fail. The lungs that were transplanted into recipients had outcomes consistent with the control group. The EVLP lungs not transplanted had decline reasons consistent with non-standard lungs assessed under ISHLT guidelines. In both studies (HELP & NOVEL) the perfusion systems used to deliver STEEN Solution™ were devices already approved and available in Thoracic surgery clinics and the components of the systems (pump, ventilator, etc) had the same principal mode of action. Hence, since the outcomes of the two trials are very similar the Novel trial validates that the XPS System™ can be safely used to evaluate lungs during STEEN Solution™.

- No clinical or statistical significance in the primary clinical parameter thirty (and 90 day) mortality demonstrated between the EVLP versus the control treatment arms in neither study.
- No indication in the secondary clinical parameters (PGD-score, ICU-stay, time on mechanical ventilator, hospital stay) that there are increased risks for

organ failure, recipient morbidity or in the measured or predicted long term mortality.

- Adverse events were generally the same for the EVLP recipients and the control recipients. None of the adverse events were determined to be associated with the EVLP procedure following review by the investigators as well as by an independent safety monitor and a safety committee.
- The noted Adverse events were not considered unexpected but typically those that you expect to see in a lung transplant recipient population after review by the investigators as well as by an independent safety monitor and a safety committee.

The two sponsored studies show that the EVLP procedure with STEEN Solution™ and the XPS System™ can safely be used in reassessing lungs in that they demonstrated that transplantation of an EVLP with STEEN Solution™ of a donor lung did not change the safety profile or the risks associated with lung transplantation to the recipient.

7.2 Probable Benefits

The probable benefit of the XVIVO Perfusion System (XPS™) with STEEN Solution™ was to increase the availability of donor lungs initially unaccepted for transplant.

- The Help trial results showed that of 22 initially unacceptable excised donor lungs, EVLP resulted in 19 lungs meeting acceptability for transplant into 19 recipients.
- The NOVEL trial results showed that of 54 initially unacceptable excised donor lungs, EVLP resulted in 29 lungs meeting acceptability for transplant into 31 recipients.
- EVLP increases the amount of time that can be taken to safely assess the suitability of a donor lung prior to transplantation.
- Because the donor lung is maintained on the XPS™, a standard integrated cardiopulmonary bypass system, additional data are provided regarding the suitability of the lung for transplant.

Therefore, the sponsored studies demonstrate that EVLP with STEEN Solution™ can increase the availability of donor organs by safely reassessing initially refused lungs after hypothermic transportation to the site of the recipient. Furthermore, the Novel trial validates that the XPS System™ is suitable as perfusion and assessment equipment with STEEN Solution™.

7.3 Summary

This report summarizes the experience of six lung transplant centers in the United States using ex vivo lung perfusion as a platform to re-assess lungs from the unused donor pool.

Patients listed for lung transplantation that agreed to participate in the study and met the inclusion/exclusion criteria were enrolled either in the EVLP or control groups.

Organ allocation followed UNOS policy. Lungs from compatible donors -blood group and donor size - where matched to the highest priority recipient based on their LAS. If the investigator determined that the donor lungs needed EVLP evaluation the recipient was informed and re-consented before transplant.

A total of 54 lungs were evaluated and 29 met the trial EVLP quality criteria and were transplanted in 31 patients. Thirty-one contemporary lung transplants using standard donors were used as controls. No significant differences were observed in terms of outcomes between the study and control group.

Graft function after transplant was evaluated using PGD grading at 0,24, and 72 hrs. At first look the EVLP group had a higher number of PGD grade 3 at 24 and 72hrs when compared to the Control group. This difference was not statistically significant and well below the ISHLT reference for both groups.

It is important to mention that patients that require ECMO support are automatically scored as PGD grade 3 independently of their graft status. In two cases, in the EVLP group, ECMO support was necessary in the operating room. One patient was put on V-A ECMO due to an aortic injury and a second patient was put on V-V ECMO because he could not tolerate single lung ventilation during the explant of his diseased lung. In both cases ECMO support was necessary before transplantation and though these patients were scored as having PGD 3 this score does not represent their graft status post transplant.

Another parameter used to evaluate graft function and or preservation is the number of airway complications that require intervention. In this study the number of airway related incidents that require interventions was not different between the patients that received an EVLP or Control lung.

Thirty-day mortality was the primary endpoint in this trial. Clinical studies in lung transplantation have used 30-day mortality as a useful parameter to evaluate lung preservation. In this study one patient died within the first 30 days post-transplant. This patient, who received a lung after EVLP evaluation, developed a serious complication after administration of ATG, which was part of the immunosuppression regime used at this institution.

Secondary endpoints such as ICU and hospital length of stay and days on mechanical ventilation were within expected for a lung transplant and showed no differences between the EVLP and Control groups. In addition variables demonstrating midterm outcomes such as pulmonary function tests and one-year survival showed no differences between the study and control groups.

In conclusion, data from this study demonstrates that the use of EVLP as a platform to evaluate lungs from the unused donor pool is safe and that we were able to transplant more patients during this study due to this device

8 Abbreviations and Definitions

Acute rejection: Graft rejection which usually begins within few days after a graft has been transplanted into a genetically dissimilar host. Lesions at the site of the graft characteristically are infiltrated with large numbers of lymphocytes and macrophages which cause tissue damage.

Airway pressures: Pressures in the bronchial system of the lung. mAwP, PAwP, platAwP Mean, peak and plateau airway pressures measured in cm H20.

Alveolar edema: An accumulation of fluid within the alveoli.

Antegrade flush: Forward flushing of the lungs for lung preservation

Atelectatic: Lack of gas exchange within alveoli, due to alveolar collapse or fluid consolidation.

Bronchiolitis Obliterans Syndrome (BOS): Chronic scarring process that affects the small airways of the lungs years after transplant surgery, results in the progressive obliteration of the small airways with resulting obstructive lung disease. BOS is a leading cause of death after the one-year anniversary of a lung transplant.

BOS grade: A grading system was used to determine how severe the BOS is in a patient.

BPM: Breaths per minute

Centrifugal pump: A rotating machine in which flow and pressure are generated dynamically.

Delta pO2: Oxygen in the pulmonary vein minus oxygen in the pulmonary artery

Deoxygenate: To remove oxygen concentration from the solution

DCD Donor: A donor after cardiac death (DCD) is a donor who has suffered devastating and irreversible brain injury and may be near death, but does not meet formal brain death criteria. In these cases, the family has decided to withdraw care. When the patient's heart stops beating, the organs are then recovered in the operating room. The surgeons involved in transplantation cannot be part of the end-of-life care or in the declaration of death.

Dynamic compliance: The value obtained when lung compliance is estimated during breathing by dividing the tidal volume by the differences in instantaneous transpulmonary pressures at the ends of the respiratory excursions, when flow in the airway is momentarily zero; this value deviates markedly from static compliance in patients in whom resistances and compliances are not uniform throughout the lung (i.e., uneven time constants).

Extra-Corporeal Membrane Oxygenator (ECMO)- Technique of providing both cardiac and respiratory support oxygen to patients whose heart and lungs are so severely diseased or damaged that they can no longer serve their function.

Endotracheal Tube (ET): A tube placed into the trachea to allow delivery of gas to the lung.

Ex Vivo Lung Perfusion (EVLP): Putting the lung from the donor and placing it onto a circuit that contains a solution that will maintain the lung.

Extended donor: Donor that does not meet the standard criteria used to determine if the donor organs can be used. Extended can mean marginal or DCD (dead of cardiac disease)

Ex vivo: Outside the body

Implantation: Suturing in of the lung into the recipient.

FiO2: Fraction of inspired oxygen, which means the percent of oxygen in each breath that is inspired.

I/E: Inspiratory to expiratory ratio

IL-6/IL-10 ;Interleukins are substances that are secreted by specific cells of the immune system, which carry signals locally between cells, and thus have an effect on other cells. This is a ratio.

In vivo: Inside the body

ISHLT: International Society of Heart and Lung Transplant (ISHLT) is comprised of Physicians, Researchers, and Nurses with over 2500 members from over 45 countries, representing over 14 different disciplines involved in the management and treatment of end-state heart and lung disease.

LA: Left Atrium-top part of the heart where the left pulmonary vein brings in oxygenated blood/solution.

Lung Allocation Score (LAS): The LAS is derived from waitlist urgency (number of days an individual is expected to live in the next year on the waitlist) and post-transplant survival (the number of days an individual is expected to live within the first year post transplant).

Lung collapse test: The trachea is disconnected from the ventilator and allowed to deflate. If the lung deflates rapidly it is the sign of good airway movement. If it takes a long time to deflate there is air trapping or moisture trapping in the lung.

Lung compliance: The measure of the tendency of the lung to recoil to its original dimensions upon removal of ventilator pressure.

LTx: Lung transplant

MAP: Mean arterial pressure -average arterial pressure during a single cardiac cycle.

Membrane gas: Membrane surface used for exchange/supply of oxygen and exchanger CO2 mmHg**.**

Organ Procurement Organization (OPO): OPOs evaluate the potential donors, check the deceased state donor registry, discuss donation with family members, contact the OPTN and run a match list, and arrange for the recovery and transport of donated organs. Upon determining donor designation and death declaration, the OPO assumes responsibility for the care of the donor.

Organ Procurement and Transplantation Network (OPTN): The unified transplant network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984. The act called for the network to be operated by a private, non-profit organization under federal contract.

pO2/FiO2: Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration OPO Organ Procurement Organization-OPOs are responsible for two main functions within their designated service area: 1) increasing the number of registered donors, and 2) coordinating the donation process when actual donors become available.

pH : A measure of the acidity or alkalinity of a solution.

PA : Pulmonary Artery-the artery that goes from the heart to the lung with deoxygenated blood.

PAF: Pulmonary artery flow in liters per minute

PAP: Pulmonary artery pressures-the measure of pressure in the pulmonary artery

PEEP: Positive end expiratory pressure- use of an elevated pressure during the expiratory phase of the ventilator cycle

PVR: Pulmonary vascular resistance- the resistance to flow offered by the vasculature of the lungs that must be overcome to push blood through the circulatory sytem in the lung.

PGD : Primary Graft Dysfunction- devastating form of acute lung injury that affects transplant patients in the first hours after they receive transplanted organs. The complication, which mimics adult respiratory distress syndrome, can be fatal.

PGD Score : A score is given based on set parameters to determine the serverity of the PGD.

Recruitment: Increasing airflow into the lungs to attempt to open up areas that have collapsed.

Reintubation: Putting the ET back into the trachea to begin ventilation

Reperfusion: During the lung transplant surgery the beginning of reperfusion is when the clamp is taken off the pulmonary artery and circulation to the "new" lung begins.

Reservoir: Hard shell container that holds the STEEN Solution™ within the perfusion circuitry**.**

Retrograde flush: Flushing backwards through the left atrium thought to remove blood clots sitting in the vasculature

Scientific Registry of Transplant Recipients (SRTR): Designs and carries out rigorous scientific analyses of data and disseminates information to the transplant community.

STEEN Solution™: The study solution-a buffered dextran and HSA containing extracellular solution with an optimal colloid pressure specifically developed for ex vivo perfusion**.**

Tidal Volume: Lung volume representing the normal volume of air displaced between normal inspiration and expiration when extra effort is not applied. Typical values are around 500ml or 7ml/kg bodyweight

United Network for Organ Sharing (UNOS): Nonprofit organization which coordinates U.S. organ transplant activities.

XVIVO Chamber: A plastic organ chamber that holds the lung during ex vivo to keep it moist and enclosed.

XVIVO Cannulas: A funnel shaped silastic tube with a pressure monitor catheter .